Answer 1:

Bibliographic Information

Ethonafide-induced cytotoxicity is mediated by topoisomerase II inhibition in prostate cancer cells. Pourpak, Alan; Landowski, Terry H.; Dorr, Robert T. Department of Pharmacology, The University of Arizona, Tucson, AZ, USA. Journal of Pharmacology and Experimental Therapeutics (2007), 321(3), 1109-1117. Publisher: American Society for Pharmacology and Experimental Therapeutics, CODEN: JPETAB ISSN: 0022-3565. Journal written in English. CAN 147:226501 AN 2007:653919 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Ethonafide is an anthracene-contg. deriv. of amonafide that belongs to the azonafide series of anticancer agents. The lack of cross-resistance in multidrug-resistant cancer cell lines and the absence of a quinone and hydroquinone moiety make ethonafide a potentially less cardiotoxic replacement for existing anthracene-contg. anticancer agents. For this study, we investigated the anticancer activity and mechanism of ethonafide in human prostate cancer cell lines. Ethonafide was cytotoxic against three human prostate cancer cell lines at nanomolar concns. Ethonafide was better tolerated and more effective at inhibiting tumor growth compared with mitoxantrone in a human xenograft tumor regression mouse model. Mechanistically, we found that ethonafide inhibited topoisomerase II activity by stabilizing the enzyme-DNA complex, involving both topoisomerase IIα and -β. In addn., ethonafide induced a potent G2 cell cycle arrest in the DU 145 human prostate cancer cell line. By creating stable cell lines with decreased expression of topoisomerase IIα or -β, we found that a decrease in topoisomerase IIα protein expression renders the cell line resistant to ethonafide. The decrease in sensitivity to ethonafide was assocd. with a decrease in DNA damage and an increase in DNA repair as measured by the neutral comet assay. These data demonstrate that ethonafide is a topoisomerase II poison and that it is topoisomerase IIα-specific in the DU 145 human prostate cancer cell line.

Answer 2:

Bibliographic Information

Antitumor activity of irofulven monotherapy and in combination with mitoxantrone or docetaxel against human prostate cancer models. van Laar, Emily S.; Weitman, Steven; MacDonald, John R.; Waters, Stephen J. Research and Development Department, MGI Pharma, Inc., Bloomington, MN, USA. Prostate (New York, NY, United States) (2004), 59(1), 22-32. Publisher: Wiley-Liss, Inc., CODEN: PRSTDS ISSN: 0270-4137. Journal written in English. CAN 141:325309 AN 2004:341654 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

BACKGROUND: Irofulven (6-hydroxymethylacylfulvene, HMAF, MGI 114) is a novel antitumor agent currently undergoing clin. trials in hormone-refractory prostate cancer. This report examines the efficacy of irofulven alone or in combination with mitoxantrone or docetaxel against androgen-independent prostate cancer cell lines. METHODS: To elucidate the activity of irofulven monotherapy and in combination, PC-3 and DU-145 cell lines were utilized in cellular viability assessments and tumor growth inhibition studies. RESULTS: Viability assays with irofulven and mitoxantrone show additive to synergistic activity. Furthermore, irofulven and mitoxantrone in combination exhibit enhanced antitumor activity against PC-3 and DU-145 xenografts. Additive combination effects are also obsd. when irofulven and docetaxel were tested against PC-3 xenografts and curative activity (8/10 CR) is obsd. in DU-145 xenografts. CONCLUSIONS: These studies demonstrate that irofulven displays strong activity as monotherapy and in combination with mitoxantrone or docetaxel against androgen-independent prostate cancer in vitro and in vivo; thus, supporting the clin. investigation of irofulven against hormone-refractory prostate cancer.

Answer 3:

Bibliographic Information

Role of drug release and liposome-mediated drug delivery in governing the therapeutic activity of liposomal mitoxantrone used to treat human A431 and LS180 solid tumors. Lim, Howard J.; Masin, Dana; Mcintosh, Natashia L.; Madden, Thomas D.; Bally, Marcel B. Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC, Can. Journal of Pharmacology and Experimental Therapeutics (2000), 292(1), 337-345. Publisher: American Society for Pharmacology and Experimental Therapeutics, CODEN: JPETAB ISSN: 0022-3565. Journal written in English. CAN 132:160802 AN 2000:17582 CAPLUS

Abstract

A previous study suggested that drug release is the dominating factor controlling biol. activity of liposomal mitoxantrone in tissues where the rate of liposome accumulation is rapid. The studies described here attempted to address the question: under conditions where the rate of liposome accumulation is slow, does drug release or liposome-mediated drug delivery become the dominant factor controlling therapeutic activity. Liposomal mitoxantrone formulations exhibiting different drug-release characteristics were injected i.v. in mice bearing human carcinoma xenografts: A431 human squamous cell carcinoma and LS180 human colon cell carcinoma in SCID/RAG 2 mice. When lipid and drug levels were measured in established (>100-mg) tumors, accumulation was more rapid in the LS180 tumors (Cmax 4 h) than in the A431 tumors (Cmax 48 h). Mean area under the curve values for mitoxantrone measured over a 96-h time course in A431 tumors were 505, 304, and 93 μg · g-1 · h-1 for 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC)/cholesterol (Chol), 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC)/Chol, and free mitoxantrone, resp. When a similar anal. was completed in LS180 tumors, the area under the curve values were 999, 749, and 251 μg · g-1 · h-1 for DSPC/Chol, DMPC/Chol, and free mitoxantrone, resp. Although drug delivery was less after administration of the DMPC/Chol liposomal mitoxantrone compared with the DSPC/Chol formulation, LS180 solid-tumor growth curves showed the treatment with the DMPC/Chol formulation produced greater delays in tumor growth compared with animals treated with the DSPC/Chol formulation. These data emphasize the importance of designing liposomal formulations that release drug after localization within a region of tumor growth.

Answer 4:

Bibliographic Information

Comparative pharmacokinetic and cytotoxic analysis of three different formulations of mitoxantrone in mice. Rentsch, K. M.; Horber, D. H.; Schwendener, R. A.; Wunderli-Allenspach, H.; Hanseler, E. Institute of Clinical Chemistry, University Hospital Zurich, Zurich, Switz. British Journal of Cancer (1997), 75(7), 986-992. Publisher: Churchill Livingstone, CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 126:301513 AN 1997:261089 CAPLUS

Abstract

Two liposomal formulations of mitoxantrone (MTO) were compared with the aq. soln. (free MTO) in terms of their pharmacokinetic behavior in ICR mice and cytotoxic activity in a nude mouse xenograft model. The three different formulations of MTO [free MTO, phosphatidic acid (PA)-MTO liposomes, pH-MTO liposomes] were administered i.v. (three mice per formulation and time point) at a dose of 4.7 μmol kg-1 for free MTO, 6.1 μmol kg-1 for PA-MTO and 4.5 μmol kg-1 for pH-MTO. The concns. of MTO were detd. using high-performance liq. chromatog. (HPLC) in blood, liver, heart, spleen and kidneys of the mice. Addnl., the toxicity and anti-tumor activity of MTO was evaluated in a xenograft model using a human LXFL 529/6 large-cell lung carcinoma. The dose administered was 90% of the max. tolerated dose (MTD) of the corresponding formulation (8.1 μmol kg-1 for free MTO, 12.1 μmol kg-1 for PA-MTO and pH-MTO). The pharmacokinetic behavior of PA-MTO in blood was faster than that of free MTO, but the cytotoxic effect was improved. In contrast, pH-MTO showed a tenfold increased area under the curve (AUC) in blood compared with free MTO, without improvement of the cytotoxic effect. This discrepancy between the pharmacokinetic and cytotoxic results could be explained by the fact that MTO in pH-MTO liposomes remains mainly in the vascular space, whereas MTO in PA-MTO liposomes is rapidly distributed into deep compartments, even more so than free MTO.

Answer 5:

Bibliographic Information

Tumor necrosis factor enhances the therapeutic effect of mitoxantrone in human ovarian cancer xenograft. Noviello, Elvira; Cimoli, Guido; Cosimi, Alessandro; Allievi, Enrico; Galletti, Piergiorgio; Parodi, Silvio; Russo, Patrizia. Department Experimental Oncology, Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy. Cytokine (1996), 8(4), 330-3. Publisher: Academic, CODEN: CYTIE9 ISSN: 1043-4666. Journal written in English. CAN 124:314766 AN 1996:257383 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The combination of tumor necrosis factor (TNF) and mitoxantrone was elevated for potential chemotherapeutic effect against a human ovarian cancer cell line A2774 heterotransplanted in female nude mice. Both antitumor efficacy (relative survival and redn. of ascites) and toxicity (wt. loss and liver toxicity) of TNF alone, mitoxantrone alone or TNF + mitoxantrone were evaluated. A significative difference was obsd. only among animals bearing tumors treated with mitoxantrone (0.012 mg/kg) + TNF (5×105 U/kg) and controls. No cytotoxic effects were obsd. for this combination. These observations provide a rationale for further evaluation of TNF + mitoxantrone based regimes for the treatment of recurrent ovarian cancer.

Answer 6:

Bibliographic Information

Hyperthermia enhances mitoxantrone cytotoxicity on human breast carcinoma and sarcoma xenografts in nude mice. Wiedemann, G.; Mella, O.; Roszinski, S.; Wiess, C.; Wagner, T. Dep. Intern., Med. Univ. Luebeck, Luebeck, Germany. International Journal of Radiation Oncology, Biology, Physics (1992), 24(4), 669-73. CODEN: IOBPD3 ISSN: 0360-3016. Journal written in English. CAN 118:428 AN 1993:428 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

In this preclin. in vivo study, we measured antitumor response, local side effects and systemic toxicity of locally applied water-bath hyperthermia given alone or simultaneously with mitoxantrone (3 mg/kg b.w. i.v.; LD 10) on a human derived breast carcinoma (MX 1) or a human sarcoma (S 117) transplanted to female athymic (nude) mice. A single hyperthermia treatment at a tumor temp. up to 43°C for 1 h caused in both tumor lines only minor tumor regressions and transient tumor growth delay. However, the antitumor effect of mitoxantrone was significantly enhanced by local hyperthermia at 42.cxa.C and particularly at 43.cxa.C. In both tumor lines, complete tumor regressions were achieved only if mitoxantrone was combined with hyperthermia. Undesired side effects and drug toxicity were not enhanced by hyperthermia. According to in vitro data and the results of the present in vivo study mitoxantrone seems to be a good candidate for clin. trials in combination with locoregional hyperthermia.

Answer 7:

Bibliographic Information

Chemosensitivity of human gastrointestinal and breast cancer xenografts in nude mice and predictability to clinical response of anticancer agents. Fujita, M.; Fujita, F.; Taguchi, T. Dep. Oncol. Surg., Osaka Univ., Osaka, Japan. Editor(s): Sordat, Bernard. Immune-Defic. Anim., Int. Workshop Immune-Defic. Anim. Exp. Res., 4th (1984), Meeting Date 1982, 311-15. Publisher: Karger, Basel, Switz CODEN: 51ONAB Conference written in English. CAN 101:103450 AN 1984:503450 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The effectiveness of 13 drugs against 14 lines of human gastrointestinal and breast cancers xenografted in nude mice was studied. Despite identical origins of organ and similarities in histol. types, degrees of differentiation, and growth rate, each line of cancer demonstrated different spectra of sensitivity to various agents. The effectiveness of various chemotherapeutic agents against human gastric cancer xenografts in nude mice was compared with the clin. effects of these drugs in clin. trials and phase II studies.

The results indicated that the nude mouse-human cancer system would be useful in preclin. secondary screening.

Answer 8:

Bibliographic Information

Clusterin knockdown using the antisense oligonucleotide OGX-011 re-sensitizes docetaxel-refractory prostate cancer PC-3 cells to chemotherapy. Sowery Richard D; Hadaschik Boris A; So Alan I; Zoubeidi Amina; Fazli Ladan; Hurtado-Coll Antonio; Gleave Martin E The Prostate Centre at Vancouver General Hospital, Vancouver, BC, Canada BJU international (2008), 102(3), 389-97. Journal code: 100886721. E-ISSN:1464-410X. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 18336596 AN 2008518100 In-process for MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

OBJECTIVES: To characterize changes in secretory clusterin (sCLU) expression in prostate cancer cells after treatment with docetaxel and to determine whether sCLU knockdown can re-introduce chemosensitivity in a docetaxel-resistant, androgen-independent human prostate cancer model. PATIENTS AND METHODS: A tissue microarray was constructed for 84 radical prostatectomy (RP) specimens from a multicentre Phase II trial of neoadjuvant combined androgen ablation and docetaxel (CUOG-P01a) and assessed for changes in the expression of the cytoprotective chaperone sCLU. The human prostate cancer cell line PC-3 was repeatedly exposed to docetaxel chemotherapy in vitro, and a docetaxel-resistant cell subline (PC-3dR) was developed and analysed. RESULTS: sCLU levels were significantly higher in RP specimens treated with neoadjuvant combined androgen ablation and docetaxel than in untreated specimens. Similarly, sCLU expression increased 2.5-fold in the newly developed docetaxel-refractory PC-3dR cell line compared with parental PC-3 cells. There was a dose-dependent and sequence-specific decrease in sCLU levels in PC-3dR cells using OGX-011, an antisense oligonucleotide against human sCLU. OGX-011 and small-interference RNA both chemosensitized PC-3dR cells to docetaxel and mitoxantrone in vitro and apoptotic rates in PC-3dR cells were significantly increased when OGX-011 was combined with docetaxel. In vivo, growth of PC-3dR xenografts in nude mice was synergistically inhibited by OGX-011 combined with paclitaxel or mitoxantrone (by 76% and 44% compared with their mismatch controls, respectively). CONCLUSION: The present findings indicate that targeted knockdown of sCLU enhances the effects of cytotoxic chemotherapy in docetaxel-refractory cells, and provide preclinical proof of principle for clinical trials testing OGX-011 in second-line chemotherapy regimens for patients with docetaxel-refractory prostate cancer.